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# Cytochrome P17 Inhibition With Ketoconazole As Treatment for Advanced Granulosa Cell Ovarian Tumor

## Case Report

A 37-year-old woman who was an active smoker with no other medical conditions and no previous pregnancies was diagnosed with a granulosa cell tumor of the left ovary in June 2002. A laparoscopic partial adnexectomy was performed in a local institution without completion of surgical stadification. In January 2006, an ipsilateral ovarian recurrence was detected. An open laparotomy mass resection plus contralateral adnexectomy, hysterectomy, pelvic and paraortic lymphadenectomy, and peritoneal sampling were performed. The anatomopathologic diagnosis was ovarian granulosa tumor, International Federation of Gynecology and Obstetrics stage IC, with a length of 10 cm and weight of 121 g. Adjuvant chemotherapy with a combination of cisplatin, etoposide, and bleomycin (BEP) was administered for three cycles. By January 2009, a unique peritoneal recurrence close to the spleen, 6 cm in length, was detected and resected. Three cycles of BEP were again administered.

On follow-up in February 2011, three peritoneal implants were found and resected without adjuvant treatment. Six months later, a new peritoneal recurrence near the liver was diagnosed, (Fig 1, arrow). No hormonal overproduction (neither estrogen nor androgens) was detected along the disease. Although inhibins have been proposed as serum markers for this tumor, their usefulness when guiding therapeutic decisions remains controversial and has not been studied.[1]

A genetic analysis was performed of the tumor that had been resected in 2006, identifying the *FOXL2* Cys134Trp (c.402C>G; Fig 2, arrow) mutation, which is patognomonic for granulosa cell tumors. Because of the short disease-free interval, resection was no longer considered an option. On the basis of the molecular consequences of such mutations, as described in the literature, ketoconazole at a dose of 400 mg three times per day plus hydrocortisone was offered. After signing written consent, the patient initiated treatment in August 2011. Ten moths later, she has not experienced progression and continues to receive ketoconazole.

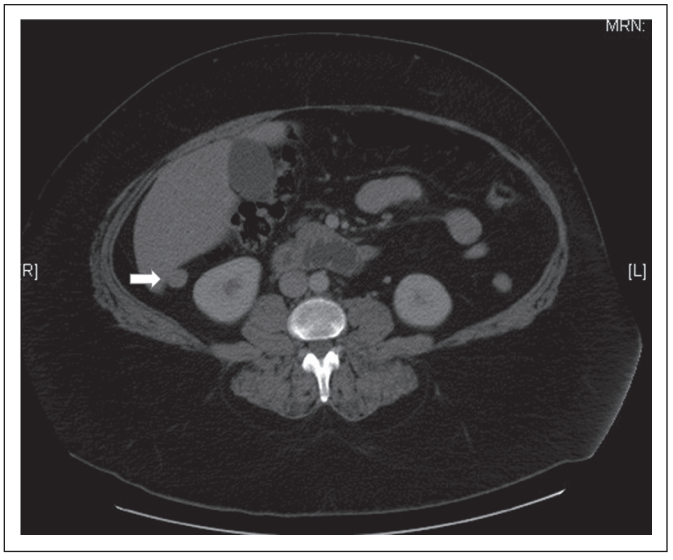


**Fig 1.**

## Discussion

Granulosa cell tumors are a rare disease with only 0.4 to 1.2 new cases per 100,000 inhabitants per year.[2] Hormonal production by the tumor (estrogens, progesterone, or androgens) can lead to some typical manifestations such as hypermenorrhea, galactorrhea, or hirsutism. Recurrences have been documented up to 10 years after first resection.

Two phase II clinical trials published in 1999 by the Gynecologic Oncology Group (GOG) and the European Organisation for Research and Treatment of Cancer, respectively, established platinum-based combinations (BEP or cisplatin, vinblastine, and bleomycin) as the cornerstone of systemic treatment.[3,4] Although partial responses were achieved in up to 60% of patients, metastatic disease continues to be a lethal condition. Currently, GOG is comparing BEP versus paclitaxel and carboplatin in a clinical trial (GOG 187).[5]

Interestingly, different hormone therapies, such as medroxyprogesterone or gonadotropin-releasing hormone agonists, have sporadically been tested.[6-9] In 1996, Fishman et al[10] treated six patients with leuprolide and achieved two partial remissions and three stabilizations.

In 2009, Shah et al[11] found, through whole-transcriptome analysis, a mutation in the *FOXL2* gene (c.402C>G [C134W]) that is now considered patognomonic of granulosa cell tumors. FOXL2 is a forkhead–winged helix transcription factor that is involved in granulosa cell development and is part of the complex AP1-Smad3-Smad4, which activates the expression of the gonadotropin-releasing hormone receptor at hipophysis.

Interestingly, the FOXL2 protein physiologically downregulates cytochrome P17 (CYP17), the enzyme that is responsible for the conversion of 17-hydroprogesterone to androstenedione. Thus, the pathologic *FOXL2* mutation (402C>G [C134W]) could potentially lead to higher levels of this protein and consequently to a rise in androstenedione levels.[12]

Because ketoconazole is a well-characterized CYP17 inhibitor, we decided to offer the patient such treatment after multiple recurrences, resections, and adjuvant treatments.[13] The patient is doing well, without progression. This encouraging experience and its molecular rationale have led the Spanish Group in Orphan and Rare Tumors (GETHI) to design a clinical trial (Granulosa et Ketoconazole, or GREKO) that will test the role of CYP17 inhibition in this tumor. If positive, multiple targeted drugs that are focused on this enzyme could easily come into the field for the treatment of this rare condition.

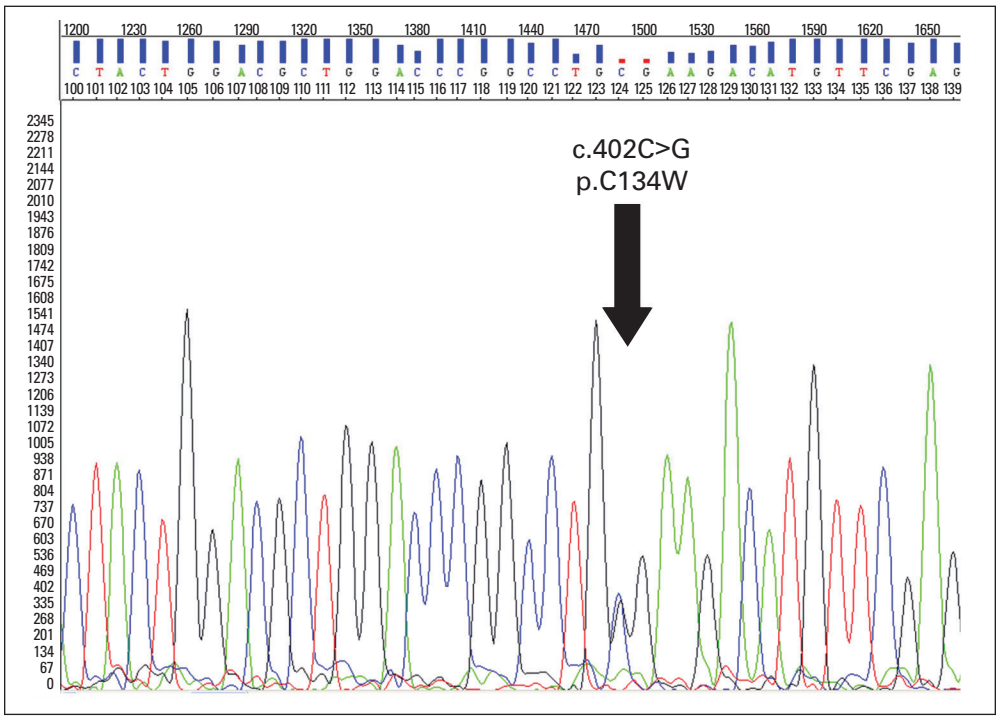


**Fig 2.**

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## AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

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